the parietal cell receptor to histamine suggests that selective blocking of the receptor to gastrin, another important secretagogue site, may be possible. Efforts in that direction have already been made.

Unfortunately, the histamine-receptor antagonists have proved to be misleading in at least two ways. First, convenience and efficacy have fostered a feeling of invincibility. The drug always seemed to work. Only slowly has it become evident that failures with histamine-receptor antagonists are both possible and more frequent than had been appreciated. Second, the drugs are remarkably (and disarmingly) effective in relieving symptoms. The prompt relief of ulcer symptoms in 48 to 96 hours after beginning therapy is the rule rather than the exception. Prospective endoscopic examinations of duodenal ulcers show that healing of an ulcer requires at least a week of treatment and that only slightly more than half are healed at the end of two weeks. Small wonder, then, that the drugs are considered uniformly effective in curing ulcers. Yet, as Mulholland and Debas have clearly stated, there remains an important clinical need to gauge when treatment with a histamine $H_2$-receptor antagonist has failed.

The epitome in specific blockage of acid secretion has been achieved with the development of the substituted benzimidazole class of drugs, exemplified by omeprazole. Omeprazole shuts down the production of hydrogen ions by the parietal cell. It does so by adhering strongly and solely to the proton pump, the producer of the ions. The drug can render patients achlorhydric for considerable periods of time. But do we really need or want to do that? It is not clear what effect such powerful agents will have on the integrity of the gastric mucosa over time. Too much of a good thing may not be too good at all.

Lastly, the perspective supplied by the authors on the surgical treatment of duodenal ulcer disease provides an important lesson on the difficulties of altering clinical practice. The attributes which lead to the wide adoption of one operative procedure but not another are not understood. In the 1970s, when parietal cell vagotomy was both widely studied and used in England and Europe, it was virtually ignored in the United States. Even now, only a few surgeons are knowledgeable and competent in this operation. Yet, in that same time-frame, jejunoileal bypass for obesity was widely practiced in the United States without benefit of much study, while being completely rejected abroad. One wonders at the discrepancy. Surgical practice much like therapy with $H_2$ blockers is not entirely directed by relevant information.

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## Bacterial Meningitis in the 1980s, or One Drug or Many?

IN THE FIRST HALF of the 1980s, we witnessed the introduction and proof of efficacy of the new group of antimicrobial agents in the treatment of the various forms of bacterial meningitis. The extensive bibliography in the article by Drs Ampel and Labadie elsewhere in this issue will inform readers of how great the activity was in this area. Such a time of change in antibiotic introduction and usage is always a confusing one. For example, moxalactam has come and gone in clinical practice without a formal obituary notice in the literature.

At this juncture several changes have clearly occurred. Chloramphenicol has been dethroned by general acclamation as an overall first- or second-line therapeutic choice for the wide range of meningeal pathogens. This drug is no longer considered appropriate for treating enteric gram-negative bacillary meningitis or for *Listeria*, and its killing kinetics for pneumococci have long been uncertain. Finally, skepticism has replaced optimism about chloramphenicol's penetration into the cerebrospinal fluid (CSF). The only uncontested area where its use still holds is in the treatment of *Hemophilus influenzae* meningitis. Meanwhile, the lightly regarded cephalosporins, whose molecules were not believed to reach the CSF, were found to reach it through inflamed meninges even more effectively than do the penicillins.[1] At this point the newer cephalosporins are considered the major agents for the treatment of bacterial meningitis.

It was not always so. Ten years ago they were considered inactive and inappropriate, which indeed they were.[2] It was not so much a question of their poor penetration into the CSF but of their lack of activity against *H influenzae*[3] and against *Neisseria* and some of the other major meningeal pathogens. This, however, was true only of that group of early cephalosporin molecules, which are now curiously termed "first-generation cephalosporins."

Cefuroxime was the first agent in this group of $\beta$-lactams to attract attention and extensive use in Europe in the treatment of meningitis,[4,5] largely on account of its strikingly enhanced activity, as compared to the older agents, against *H influenzae* and *Neisseria*. It was used both as therapy for enteric gram-negative pathogens and as empiric initial therapy in pediatric meningitis. Nevertheless, some caution was voiced in the beginning about its therapeutic margin of safety for the common meningeal pathogens. This translates into how many multiples of the minimal inhibitory concentration or, better yet, the minimal bactericidal concentration of the potential pathogens are possibly attainable in the CSF. Because miscalculated, late or missed doses are always possible, and indeed even likely, prudence can be important in designing antibiotic therapy. Indeed, several poor responses to cefuroxime therapy have been recently reported.[6] The introduction and widespread clinical use of cefotaxime and subsequently of ceftriaxone, whose enhanced activity provides a far higher therapeutic margin, have rendered further debate irrelevant. Enteric gram-negative meningitis ranks a poor fourth, in comparison to *Streptococcus pneumoniae, H influenzae,* and *Neisseria meningitidis,* as a meningeal pathogen in this country. Nevertheless, it was in this area of usage that cefotaxime and moxalactam showed their usefulness, probably as a consequence of the newly demonstrated lack of effectiveness of chloramphenicol.[7] Today cefotaxime and, by extension, ceftriaxone are considered the agents of choice for the group of pathogens comprising *Escherichia coli, Klebsiella, Salmonella* and the proteus group.[8] For *Enterobacter,* the results are less good; at least half of the cases fail to respond.[8] It is here that trimethoprim-sulfamethoxazole or gentamicin given intrathecally (or both therapies) can be extremely useful. *Pseudomonas* meningitis, usually a sequela of prolonged neurosurgical procedures, can often be successfully treated with ceftazidime, prudently supplemented by gentamicin parenterally or, better, intrathecally, since relapses have occurred with the use of ceftazidime as monother-

apy.[9] Further, ceftazidime monotherapy for infections of other body sites has led to the emergence of strains of *Pseudomonas* resistant to this drug.[10]

The present state of things has been ably summarized in Table 1 of the article by Ampel and Labadie. Other considerations pertain in Europe, where the primary therapeutic approach is often that of using cefotaxime as initial empiric therapy for all cases of meningitis before isolation and sensitivity testing of the organism.[11,12] A similar pattern of use was previously noted for cefuroxime in the same area. There is a problem in this form of therapy. None of the available cephalosporins are adequately active against *Listeria monocytogenes,* an infrequent meningeal pathogen in this country (although several recent dairy outbreaks may eventually challenge this generalization). In the dairy farm areas along Europe's northeastern coast, *L monocytogenes* is an important pathogen in neonates, pregnant women and immunosuppressed patients. We have asked several colleagues from that area what they do in this circumstance. Apparently for such high-risk groups, they just add amoxicillin to the cefotaxime regimen.

How can one explain this radical difference in patterns of antibiotic use? Our European colleagues make the following points: First, the limitations of the newer cephalosporins—that is, lack of effectiveness against *Listeria* and enterococci—are minor compared with the limitations of ampicillin (amoxicillin) or chloramphenicol. Second, the age-related separation of pathogens is hardly absolute. Adults can have *Salmonella* or *H influenzae,*[13] just as children can have pneumococcal meningitis.[12,14] Last, the ordinary diagnostic measures that we recommend in cases of meningitis are subject to error. A far higher percentage of cases than we would like to admit has negative Gram's stains or fails to produce positive cultures. Immunologic methods are most useful for *H influenzae* meningitis, but of little help for other forms of meningitis. Even when smears are positive, the correct diagnosis may not be made. Another reason for this difference in practice may lie in the nature of the clinical practice of pediatrics or infectious disease in large parts of Western Europe as compared with the United States. The separation of the hospital from office practice has progressed much further in Europe than it has in the United States. The hospital staff is full time, the hospitals are quite large and the infectious disease and pediatric specialists often have primary responsibility for 50 to 100 beds in the larger centers. In short, after the nth case of meningitis, what does one want with a complicated therapeutic schema? In this country few infectious disease specialists or pediatricians have primary clinical care responsibility for more than a few such cases each year. Hence, complicated schemas are possible. If my observations are correct, we should detect a future tendency toward a unitary initial therapy in the larger clinical centers in this country. Perhaps in a few years' time, Ampel and Labadie will again have to revise their therapy table, signifying an even greater change in antibiotic usage.

In summary, the past five to ten years have been a period of considerable change in our patterns of use of antibiotics for meningitis. Cephalosporins achieve significant antibiotic concentrations in the CSF of patients with meningitis, and several have sufficient activity to be of broad use in treating the four most common meningeal pathogens: pneumococci, *H influenzae,* meningococci and the enteric gram-negative rods. Chloramphenicol is now viewed as having a limited role and that only in treating bacteria for which it is bactericidal. Indeed, it is now conceded that to successfully treat meningitis (as to treat endocarditis) one must choose a bactericidal drug. Well, almost always! Those *Listeria* again! Neither ampicillin nor penicillin is reliably bactericidal for *L monocytogenes,* at least in the concentrations achievable in the CSF.[15,16] An aminoglycoside needs to be added to achieve that in the test tube. Yet, ampicillin and penicillin work even as monotherapy, and it is hard to show that adding an aminoglycoside clinically changes the response rate.[7]

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## The Chief Complaint

IN PATIENT CARE the "chief complaint" gives the first indication of why a patient may be seeking a physician's help. Sometimes the chief complaint relates to the obvious. "I cut my finger." "I am allergic to cats but I love my cat." But sometimes the relationship between the chief complaint and what is really wrong may not be so direct or obvious. "I have a pain in my belly." "I have headaches all the time." "I have pains around my heart." And if one is privileged to take care of a physician or a nurse, the chief complaint and the description of symptoms (1) may be a model of professional accu-